PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IBT1.073-WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/27116	International filing date *(day/month/year)* 20 August 2004 (20.08.2004)	Priority date *(day/month/year)* 20 August 2003 (20.08.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61N 5/00 and US Cl.: 600/1-8		
Applicant INTERNATIONAL BRACHYTHERAPY		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) ____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28-July-2005 (28.07.2005)	31 October 2005 (31.10.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Samuel G. Gilbert Telephone No. 866-217-9197

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/27116

Box No. I Basis of the report

1. With regard to the language, this report is based on:

☐ the international application in the language in which it was filed.

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "origin ally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1-13 and 15-17 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* 14 received by this Authority on 28 July 2005 (28.07.2005)

☒ the claims:
pages NONE as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* 18-22 received by this Authority on 28 July 2005 (28.07.2005)

☒ the drawings:
pages 1/5-5/5 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☒ the claims, Nos. 27-41
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/27116

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 2-15, 18-19, 22-26	YES
	Claims 1, 16, 17, 20, 21	NO
Inventive Step (IS)	Claims 2, 7-15, 18, 19, 24-26	YES
	Claims 1, 3-6, 16, 17, 20-23	NO
Industrial Applicability (IA)	Claims 1-26	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1, 16, 17, and 21 lack novelty under PCT Article 33(2) as being anticipated by McIntire et al (6,632,176). The applicant argues that McIntire et al teaches the use of a separate marker(roughening the surface). It is the examiner's position that this marker is for ultrasonic imaging not x-ray or fluoroscopic imaging. Therefore no additional marker is required for those types of imaging.

Claims 1 and 20 lack novelty under PCT Article 33(2) as being anticipated by Kaplan(2002/0058057). The applicant argues that the Kaplan does not teach an isotope substantially uniformly mixed in a carrier. Applicant's attention is invited to paragraph[0050].

Claims 3-6, and 22-23 lack an inventive step under PCT Article 33(3) as being obvious over McIntire et al(6,632,176) in view of Slater et al(6,273,851). McIntire teaches a device and method as claimed but does not teach a socket or universal joint for connecting spacers and forming linear strands. Slater teaches using sockets element -48a- in figure 3 to connect seeds and spacers to form a linear strand. It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the sockets taught by Slater et al on the seeds of McIntire to provide a seed train that can be linked together under and coherently maneuvered under both compressive and tensile forces as taught by Slater et al.

Claim 2, 7-15, 18, 19 and 24-26 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest The prior art doe not teach or fairly suggest using PEEK or a high density material to form the seed, further no malleable plug is taught connected to the capsule to retain the capsule in a needle as claimed. Regarding claims 37-41 the prior art does not teach or fairly suggest a method of making including injecting the homogenous radioactive mixture through an ink-jet head into the cylindrical mold.

Claims 1-26 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/US04/27116

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 5 depends in one version on claim 6 which depends fropm claim 5, Therefore 5/6 is is impropper.

polyethylene and polypropylene. The high melting temperature of poly ether ether ketone (PEEK, 343 degrees Celsius) makes this a preferred choice, especially if high temperatures are expected to be encountered, e.g. in sterilization. However, there are many other plastic materials which those skilled in materials science will find to be appropriate and satisfactory for a variety of different applications, including biodegradable polymer materials known for this purpose.

Composition of Radioactive Source Material for a Pd^{103} Seed of the Current Invention

The following example is intended to illustrate the formulation of a source material that is essentially free of internal x-ray absorption and is thus produced from carrier free Pd^{103} from a proton accelerator. Many persons skilled in the art are familiar with methods for extracting Pd^{103} from rhodium cyclotron targets and its subsequent purification. An example includes Carden, U.S. Patent 5,405,309. At the end of the purification process, the solution containing the Pd^{103} is concentrated into a very small mass of material, for instance 25 Ci of Pd^{103} contained in a final mass of approximately 200 mg. This concentration step is necessary for two reasons: 1) because the volume available within the seed for the source material to occupy is very small (approximately 0.8 μL), the Pd^{103} activity per unit of source material must be correspondingly large (approximately 20 Ci per ml) and 2) the radioactive concentrate acts as a diluent in the solidified polymer, and if this effect is too large, the curing properties and mechanical strength of the cured polymer may be adversely modified.

A desirable property of the source material is that it solidifies into a hard and durable "pellet" once it has been delivered to the desired location within the seed. To satisfy this requirement, we have developed an epoxy formulation with thermally initiated polymerization.

Finally, delivery of the source material into the desired location within the seed is problematic. When considered in relative terms, the problem can be summarized as the necessity to deliver a very precise volume of fluid to the bottom of a long narrow cavity. A solution to this problem is to use a single-jet, drop-on-demand, fluid-jet print head to deliver a precise number of drops into the cavity of the seed shell. This however adds the requirement that the source material must have a viscosity and surface tension that will facilitate jetting. Given below are two examples of formulations found to satisfy the aforesaid requirements (percentages being weight percent):

Formulation 1

1. Radioactive residue (17 wt. %)
2. Triethylene glycol divinyl ether (55 wt. %)

1. An implantable brachytherapy source comprising a sealed capsule of mechanically strong, biocompatible plastic material that is transparent to therapeutic radiation, containing a source of therapeutic radiation consisting essentially of a radioactive isotope substantially uniformly mixed in a carrier consisting essentially of a substance that is resistant to radiation polymerization in a fluid phase and has been induced to solidify by raising its temperature, the radioactive isotope being selected from the group: Pd-103, I-125, Cs-131.

2. The implantable brachytherapy source of Claim 1 wherein the capsule is made from medical grade PEEK.

3. The implantable brachytherapy source of Claim 1 having a plurality of connecting configurations as an integral part of the capsule, such that it accommodates attaching functional units to form linear strands and planar arrays of sources and functional units.

4. The implantable brachytherapy source of Claim 1 wherein one or more of the plurality of connecting configurations has a spherical wall defining a deformable socket adapted to connect with a ball joint on a functional unit to facilitate connection and disconnection of the source and functional units.

5. A biocompatible, biodegradable functional unit having 1, 3, 4 or 6 connecting ends which are adapted to connect with one or more brachytherapy sources having a plurality of connecting configurations as an integral part thereof, to form planar arrays of sources and functional units.

6. A functional unit of Claim 5 wherein one or more of the connecting ends comprises a ball joint adapted to connect with a brachytherapy source having a socket therein; the ball joint comprising a ball element having a slit formed therein to facilitate connection and disconnection of such a source and the functional unit.

7. A functional unit of Claim 5 wherein it controllably releases one or more medicines.

8. A functional unit of Claim 5 wherein the one or more medicines it controllably releases are selected from the group consisting of anti-inflammatory drugs, local anesthetics, antibiotics, anti-cancer adjuvants and radiation enhancing drugs.

9. A functional unit of Claim 5, comprising material that absorbs radio waves to produce heat, making possible an effective means of adding hyperthermia to the radiation treatment of the target organ.

10. A biocompatible, biodegradable functional unit having a single connecting end, the functional unit being adapted to connect with a brachytherapy source at the head of a train of

brachytherapy sources having a plurality of connecting configurations as an integral part thereof, the functional unit being adapted for use with a brachytherapy source insertion needle having an interior wall, the functional unit being a malleable plug comprising a retaining element depending on interference with the interior wall of the brachytherapy source insertion needle, so that the train of brachytherapy sources will only leave the needle as a result of force applied on the brachytherapy source insertion needle by a therapist, the plug comprising plastic foam such that it is readily imaged with ultrasound so the first seed leaving the needle can be detected.

11. The functional unit of Claim 10 wherein the single connecting end comprises a ball joint adapted to connect with a brachytherapy source having a socket therein; the ball joint comprising a ball element having a slit formed therein to facilitate connection and disconnection of such a source and the functional unit.

12. A method of making a brachytherapy source of Claim 1, wherein said substance that is resistant to radiation polymerization in a fluid phase is an epoxy-based fluid, comprising the steps of: substantially uniformly mixing the epoxy-based fluid with the radioisotope to form a liquid that can be jetted through an ink-jet head; jetting the liquid through an ink-jet head into a plastic capsule casing; and heating the contents of the plastic capsule casing, thereby initiating curing.

13. The method of Claim 12 where the epoxy-based fluid has the formulation:(percentages are weight percent):

(1) Radioactive residue 17%

(2) Triethyleneglycoldivinylether 55%

(3) Epoxy resin 18%

(4) Borontrifluoride monoethylamine 2%

(5) Propylene carbonate 8%; further comprising:

(a) dissolving radioactive residue in Triethyleneglycoldivinylether and Cycloaliphatic epoxide resin,

(b) dissolving Borontrifluoride monoethylamine in a portion of Polylene carbonate solvent;

(c) combining the liquids of (a) and (b) above to form the source material;

(d) injecting the source material into the plastic capsule casing and heating to approximately 190°C to initiate curing in the capsule casing.

14. A method of making a brachytherapy source of Claim 1, wherein said substance that is resistant to radiation polymerization in a fluid phase is an epoxy based fluid, comprising the steps of: substantially uniformly mixing the epoxy based fluid with the radioisotope to form a liquid that can be jetted through an ink-jet head; jetting the liquid into a separate mold, heating the contents of the separate mold, thereby initiating curing.

15. The method of Claim 14 where the epoxy based fluid has the formulation:(percentages are weight percent):

(1) Radioactive residue 17%

(2) Triethyleneglycoldivinylether 55%

(3) Epoxy resin 18%

(4) Borontrifluoride monoethylamine 2%

(5) Propylene carbonate 8%; further comprising:

(a) dissolving radioactive residue in Triethyleneglycoldivinylether and Cycloaliphatic epoxide resin,

(b) dissolving Borontrifluoride monoethylamine in a portion of Polylene carbonate solvent;

(c) combining the liquids of (a) and (b) above to form the source material;

(d) injecting the source material into a mold and heating to approximately 190°C to initiate curing within the separate mold .

16. An implantable source of therapeutic radiation comprising a sealed capsule with a plastic carrier consisting essentially of radioisotope co-mingled with enough non-radioactive isotope such that the resulting carrier is visible with fluoroscope or x-ray film negating the need for a separate marker, but which remains sufficiently transparent to the curative radiation to be a practical therapeutic device.

17. The implantable source of Claim 16 wherein the transmission of therapeutic radiation is between 20% and 80%.

18. The implantable source of Claim 16 wherein the radioisotope is Pd-103, produced by neutron activation in a nuclear reactor and the non-radioactive isotope consists essentially of the remaining stable Pd isotopes, augmented by addition of high specific activity Pd-103 or non-radioactive palladium, to adjust the transmission of radiation through the carrier.

AMENDED SHEET

19. The implantable source of Claim 16 wherein the radioisotope is I-125, non-radioactive isotope consists essentially of non-radioactive iodine, or other chemically compatible heavy element, added to adjust the transmission of radiation through the carrier.

20. The implantable brachytherapy source of Claim 1 wherein the radioisotope is I-125, augmented by addition of non-radioactive iodine, or other chemically compatible heavy element, to adjust the transmission of radiation through the carrier.

21. An implantable brachytherapy source comprising: a sealed capsule of mechanically strong, biocompatible plastic material that is transparent to therapeutic radiation, containing a source of therapeutic radiation consisting essentially of the radioactive isotope Cs-131 substantially uniformly mixed with and dispersed throughout a biocompatible nonabsorbable polymeric matrix.

22. The implantable brachytherapy source of Claim 21 having a a plurality of connecting configurations as an integral part of the capsule, such that it accommodates attaching functional units to form linear strands and planar arrays of sources and functional units.

23. The implantable brachytherapy source of Claim 22 wherein one or more of the plurality of connecting configurations has a spherical wall defining a deformable socket adapted to connect with a ball joint on a functional unit to facilitate connection and disconnection of linear strands and planar arrays of the source and functional units.

24. A method of making a source of therapeutic radiation of the implantable brachytherapy source of Claim 21, comprising the steps of:

(a) mixing radioactive isotope Cs-131 dispersed in a solvent, with a biocompatible nonabsorbable polymeric matrix to form a fluid homogenous mixture;

(b) injecting said fluid homogenous radioactive mixture through an ink-jet head into a mold;

(c) heating the mold to cure the fluid homogenous radioactive mixture into a solid radioactive form;

(d) removing the cured solid radioactive form from the mold.

25. The method according to Claim 24, wherein the cured solid radioactive form is encased within a thin layer of biocompatible nonabsorbable polymeric matrix to seal.

26. The method according to Claim 25, wherein the biocompatible nonabsorbable polymeric matrix is selected from the group consisting of high density polyethylene, high density polyaryletheretherketone or medical grade polyaryletheretherketone.

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26. The method according to Claim 25, wherein the biocompatible nonabsorbable polymeric matrix is selected from the group consisting of high density polyethylene, high density polyaryletheretherketone or medical grade polyaryletheretherketone.

AMENDED SHEET